



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB99/02588 (22) International Filing Date: 6 August 1999 (06.08.99) (30) Priority Data: <table border="0"> <tr><td>9817315.6</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817310.7</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817337.0</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817308.1</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817311.5</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817313.1</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817323.0</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817338.8</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817312.3</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817367.7</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817324.8</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817314.9</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817335.4</td><td>8 August 1998 (08.08.98)</td><td>GB</td></tr> <tr><td>9817318.0</td><td>10 August 1998 (10.08.98)</td><td>GB</td></tr> <tr><td>9817319.8</td><td>10 August 1998 (10.08.98)</td><td>GB</td></tr> <tr><td>9823834.8</td><td>30 October 1998 (30.10.98)</td><td>GB</td></tr> </table> (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		9817315.6	8 August 1998 (08.08.98)	GB	9817310.7	8 August 1998 (08.08.98)	GB	9817337.0	8 August 1998 (08.08.98)	GB	9817308.1	8 August 1998 (08.08.98)	GB	9817311.5	8 August 1998 (08.08.98)	GB	9817313.1	8 August 1998 (08.08.98)	GB	9817323.0	8 August 1998 (08.08.98)	GB	9817338.8	8 August 1998 (08.08.98)	GB	9817312.3	8 August 1998 (08.08.98)	GB	9817367.7	8 August 1998 (08.08.98)	GB	9817324.8	8 August 1998 (08.08.98)	GB	9817314.9	8 August 1998 (08.08.98)	GB	9817335.4	8 August 1998 (08.08.98)	GB	9817318.0	10 August 1998 (10.08.98)	GB	9817319.8	10 August 1998 (10.08.98)	GB	9823834.8	30 October 1998 (30.10.98)	GB	(72) Inventors; and (75) Inventors/Applicants (for US only): CROWE, David [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). MOORE, Stephen [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). O'KEEFFE, Deirdre [IE/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). URQUHART, Michael [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). (74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	
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(54) Title: PAROXETINE SALTS																																																			
(57) Abstract																																																			
<p>A salt of paroxetine with an acid selected from the group consisting of hydrobromic, hydroiodic, hexanoic, malic, aspartic, adipic, palmitic, stearic, ethylenediaminetetraacetic (EDTA), naphthoic, naphthalenesulphonic, pamoic, gluconic, salicylic, hydroxynaphthoic and hydroxybutyric acids, is useful in the treatment and prophylaxis of certain CNS disorders.</p>																																																			

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## PAROXETINE SALTS

5 The present invention relates to novel compounds, to processes for preparing them and to their use in treating medical disorders.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-)-*trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-  
10 phenoxymethyl)-piperidine. This compound is used in therapy as the hydrochloride salt for the treatment and prophylaxis of *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

We have now surprisingly discovered novel salts of paroxetine which may be used as an  
15 alternative to the currently marketed hydrochloride, or as an intermediate in the preparation of the hydrochloride.

According to the present invention there is provided a novel salt of paroxetine with an acid selected from the group consisting of hydrobromic, hydroiodic, hexanoic, malic, aspartic,  
20 adipic, palmitic, stearic, ethylenediaminetetraacetic (EDTA), naphthoic, naphthalenesulphonic, pamoic, gluconic, salicylic, hydroxynaphthoic and hydroxybutyric acids.

Malic, aspartic and gluconic acids exist in enantiomeric forms and this invention includes  
25 salts with both the D and L-acids and racemic mixtures thereof.

Malic, aspartic, adipic, EDTA and pamoic acids are dibasic and the invention therefore includes both salts in which the ratio of paroxetine to acid (by mole) is 1:1 and salts in which the ratio of paroxetine to acid (by mole) is 2:1, as well as mixed salts with, for  
30 example, an alkali metal or ammonium cation.

Salts of this invention with naphthoic acid include paroxetine 1- or 2-naphthoate; salts with naphthalenesulphonic include paroxetine 1- or 2-naphthalene sulphonate; salts with

hydroxynaphthoic include salts of paroxetine with 2-hydroxy-1-naphthoic acid, 1-hydroxy-2-naphthoic acid, 6-hydroxy-2-naphthoic acid, 6-hydroxy-1-naphthoic acid or 3-hydroxy-2-naphthoic acid; salts with hydroxybutyric acid include paroxetine 4-hydroxybutyrate.

- 5 In one aspect the novel salts of this invention are provided in non-crystalline form, which may take the form of a solid or an oil. The oil is preferably absorbed on a solid carrier, especially a carrier that is usable as a component of a pharmaceutical composition.

- 10 In another aspect the novel salts of this invention are provided in crystalline form. When the crystalline form exists as more than one polymorph, each polymorph forms another aspect of this invention.

- Paroxetine salts may be prepared by contacting stoichiometric amounts of the acid (enantiomer or racemic mixture) and paroxetine free base. Alternatively the acid may be used in excess, usually no more than 1.5 equivalents. Preferably the base and/or the acid is in solution, more preferably both are in solution. Mixed salts can be prepared by forming the precursor 1:1 or hydrogen salt (of paroxetine with the acid, or the metal or ammonium ion with the acid) in situ, or using it preformed in solution, and contacting it in solution with a solution containing the metal or ammonium ion, or treating a metal or ammonium hydrogen malate with paroxetine.

- Most commonly used solvents are suitable for mobilising paroxetine free base, for example toluene, alcohols such as methanol, ethanol, propan-2-ol, esters such as ethyl acetate, ketones such as acetone and butanone, halogenated hydrocarbons such as dichloromethane, and ethers such as tetrahydrofuran and diethyl ether. The concentration of paroxetine base is preferably in the range 5 to 50% weight/volume, more preferably in the range 10 to 30%.

- Suitable solvents for the acids used in accordance with the present invention include water, lower alcohols such as methanol, ethanol and isopropanol, ethers such as diethyl ether and tetrahydrofuran, hydrocarbons such as toluene and benzene, esters such as ethyl acetate, ketones such as acetone, butanone and isobutyl methyl ketone, and halogenated hydrocarbons such as chloroform.

Hydrogen bromide is preferably used in the form of an aqueous solution, for example the commercially available 48% aqueous solution, but may also be used in more dilute solutions, optionally further diluted with a miscible organic solvents. Hydrogen bromide may be also be added in the form of a gas; this method is particularly appropriate when it is  
5 desired to prepare the paroxetine salt in an anhydrous solvent system. The concentration of hydrogen bromide in non-aqueous solutions is preferably in the range 0.1 to 9 molar, preferably between 1 and 3 molar.

Hydrogen iodide is preferably used in the form of an aqueous solution, for example the  
10 commercially available 47% or 55% aqueous solutions, but may also be used in more dilute solutions, optionally further diluted with a miscible organic solvents. The concentration of hydrogen iodide in non-aqueous solutions is preferably in the range 0.1 to 7.6 molar, preferably between 1 and 3 molar.

15 Hexanoic acid is miscible with most solvents.

Malic acid is preferably added as a solid or in solution, for example in water, ethers such as diethyl ether or tetrahydrofuran, a ketone such as acetone, or a lower alcohol such as  
methanol, ethanol, or propan-2-ol, or a mixture of solvents. The concentration of malic acid  
20 solutions are preferably in the range 0.1 to 4 molar, preferably between 1 and 2 molar.

The most suitable solvent for aspartic acid is water. Aspartic acid may be used either as a solid or in solution, suitable concentrations being in the range 0.01 to 1 molar, preferably  
between 0.1 and 0.5 molar.

25 Adipic acid is preferably added as a solid or in solution, for example in water (at elevated temperatures), acetone, or a lower alcohol such as methanol, ethanol, or propan-2-ol, or a mixture of solvents. The concentration of adipic acid solutions are preferably in the range 0.1 to 4 molar, preferably between 1 and 2 molar.

30 Palmitic acid is preferably added as a solid or in solution, for example in toluene, ether, acetone, or a lower alcohol such as methanol, ethanol, or propan-2-ol, or a mixture of

solvents. The concentration of palmitic acid solutions are preferably in the range 0.1 to 2 molar, preferably between 0.5 and 1 molar.

5 Stearic acid is preferably added as a solid or in solution, for example in toluene, acetone, or a lower alcohol such as methanol, ethanol, or propan-2-ol, or a mixture of solvents. The concentration of stearic acid solutions are preferably in the range 0.1 to 2 molar, preferably between 0.5 and 1 molar.

10 EDTA is preferably added as a solid or in solution, for example in hot water, or lower alcohol such as methanol, ethanol, or propan-2-ol, or a mixture of solvents. The concentration of ethylenediaminetetraacetic acid solutions are preferably in the range 0.1 to 2 molar, preferably between 0.5 and 1 molar.

15 Naphthoic acid is preferably added as a solid or in solution, for example in an ether such as diethyl ether or tetrahydrofuran, or a lower alcohol such as methanol, ethanol, or propan-2-ol, or a mixture of solvents. The concentration of naphthoic acid solutions are preferably in the range 0.1 to 2 molar, preferably between 0.3 and 1 molar.

20 The 1- or 2-naphthalene sulphonic acid is preferably added as a solid or an aqueous or lower alcoholic or toluene solution optionally further diluted with a miscible organic solvent. The concentration of 1- or 2-naphthalene sulphonic acid solutions are preferably in the range 0.1 to 3 molar, preferably 0.5 to 1.5 molar.

25 Pamoic acid is preferably added as a solid or in solution, for example in chloroform or pyridine, or a mixture of solvents. The concentration of pamoic acid solutions are preferably in the range 0.05 to 1 molar, preferably between 0.1 and 0.3 molar.

30 Gluconic acid is preferably added as an aqueous solution optionally further diluted with a miscible organic solvent. The concentration of gluconic acid is preferably in the range 0.1 to 4 molar, preferably 1 to 3 molar.

The hydroxynaphthoic acids are preferably added as a solid or in solution, for example in an ether such as diethyl ether or tetrahydrofuran, or a lower alcohol such as methanol,

ethanol, or propan-2-ol, or benzene, or toluene, or a mixture of solvents. The concentration of hydroxynaphthoic acid solutions are preferably in the range 0.1 to 2 molar, preferably between 0.3 and 1 molar.

- 5 Salicylic acid is preferably added as a solid or in solution, for example in water or an ether such as diethyl ether or tetrahydrofuran, a ketone such as acetone, butanone, or isobutyl methyl ketone, chloroform, toluene, or a lower alcohol such as methanol, ethanol, or propan-2-ol, or a mixture of solvents. The concentration of salicylic acid solutions are preferably in the range 0.1 to 4 molar, preferably between 0.5 and 2 molar.

10

In the case of 4-hydroxybutyric acid, a double decomposition approach may be employed in which a salt of 4-hydroxybutyric acid, for example the sodium salt, is contacted in solution with a salt of paroxetine, for example the hydrochloride salt. The salts are preferably chosen so that the by-product salt (sodium chloride, in the example) is readily removed from solution. This approach is particularly convenient as a result of the tendency of 4-hydroxybutyric acid to form a lactone. Acid salts of paroxetine may be dissolved in a wide range of solvents, including water, alcohols, ketones, hydrocarbons, chlorinated hydrocarbons, esters and ethers. Particularly suitable solvents for paroxetine hydrochloride are methanol, propan-2-ol, dichloromethane, toluene and acetone. The 4-hydroxybutyric acid or salt thereof is preferably added to a solution of paroxetine free base or its salt as a solid or in solution, for example in water or an ether such as diethyl ether or tetrahydrofuran, a ketone such as acetone, butanone, or isobutyl methyl ketone, or a lower alcohol such as methanol, ethanol, or propan-2-ol, or a mixture of solvents. The concentration of 4-hydroxybutyric acid solutions are preferably in the range 0.1 to 5 molar, preferably between 0.5 and 2 molar.

25

In general, elevated temperatures may be used to enhance solubility. The acids may also be used in the form of a soluble salt such as the ammonium salt or a salt of an amine, for example ethylamine or diethylamine.

30

The paroxetine salts may be isolated in solid form by conventional means from a solution thereof obtained as above. For example, the non-crystalline salts may be prepared by

precipitation, spray drying, and freeze drying of solutions, or vacuum drying of oils, or solidification of melts obtained from reaction of the free base and the acid.

5 The crystalline salts may be prepared by directly crystallising from a solvent in which the product has limited solubility, or by triturating or otherwise crystallising a non-crystalline salt. An improved yield of the salt is obtained by evaporation of some or all of the solvent or by crystallisation at elevated temperature followed by controlled cooling, preferably in stages. Careful control of precipitation temperature and seeding may be used to improve the reproducibility of the production process and the particle size distribution and form of  
10 the product.

An alternative method of preparing paroxetine salts is to start with a salt of paroxetine with an organic acid, such as acetic acid or maleic acid. Use of another salt of paroxetine as a starting material is suitable for preparation of the crystalline salt or, if a volatile acid such  
15 as acetic acid is used, non-crystalline salts by methods that involve evaporation (such as freeze-drying and spray-drying).

Prior to the isolation of the paroxetine salt, water may be removed by azeotropic distillation to avoid the formation of hydrates or to obtain the product in anhydrous form. In that case,  
20 suitable solvents for the solution of the salt are those which form an azeotrope with water, such as toluene, pyridine, isopropanol, isobutyl methyl ketone and xylene. It should also be appreciated that mixtures of solvents can also be used to aid the azeotropic removal of water.

25 More generally, crystallization may be carried out from any solvent which allows formation of the desired crystal structure, using seeds of the desired structure where necessary or desirable. Clearly it is convenient where possible to crystallise from the solvent used for salt formation. When polymorphs exist, individual polymorphs are preferably crystallized directly from a solution of the salt, although recrystallizing a solution of one polymorph  
30 using seeds of another polymorph may also be carried out.

More particularly:



paroxetine hydrobromide may be recrystallised from a variety of organic solvents, such as propan-2-ol, acetone, or tetrahydrofuran;

paroxetine hydriodide may be recrystallised from a variety of organic solvents, for example toluene or ethyl acetate;

5 paroxetine hexanoates can be recrystallised from solvent systems which are suitable for its preparation, for example toluene and acetonitrile;

paroxetine malates can be recrystallised from solvent systems which are suitable for its preparation, for example acetone, ethyl acetate, and acetonitrile;

10 paroxetine adipates can be recrystallised from solvent systems which are suitable for its preparation, for example toluene, acetone, or lower alcohols followed by precipitation with ethyl acetate, ether, or hexane; alternatively, paroxetine adipate may be recrystallised by cooling and optionally seeding hot solutions in suitable solvents such as butan-1-ol or acetonitrile;

15 paroxetine palmitates and stearates can be recrystallised from solvent systems which are suitable for its preparation, for example toluene, acetone, ethyl acetate, acetonitrile, or lower alcohols optionally with an additional solvent to decrease solubility, for example diethyl ether or hexane;

paroxetine ethylenediaminetetraacetates can be recrystallised from solvent systems which are suitable for its preparation, for example toluene, water, or lower alcohols;

20 paroxetine naphthoates can be recrystallised from solvent systems which are suitable for its preparation, for example toluene and propan-2-ol, optionally adding a second solvent, for example diethyl ether, to reduce the solubility;

25 paroxetine 1- or 2-naphthalene sulphonate may be recrystallised from water or a variety of organic solvents, such as toluene and propan-2-ol, optionally adding a second solvent, for example diethyl ether, to induce crystallization;

paroxetine pamoates can be recrystallised from solvent systems which are suitable for its preparation, for example chloroform or pyridine;

paroxetine gluconate may be recrystallised from a variety of organic solvents, such as acetone and butanone;

30 paroxetine hydroxynaphthoates can be recrystallised from solvent systems which are suitable for its preparation, for example acetone, toluene, and propan-2-ol;

paroxetine salicylates and paroxetine 4-hydroxybutyrates can be recrystallised from solvent systems which are suitable for its preparation.

The salt may obtained as a solvate or hydrate, when during isolation from solution it becomes associated with the solvent in which it is dissolved. Any such solvate or hydrate forms a further aspect of this invention. Solvates may be returned to the unsolvated salt by heating, for example by oven-drying, or by treatment with a displacement solvent which  
5 does not form a solvate.

Paroxetine free base may be prepared according to the procedures generally outlined in US Patent No 4,007,196 and EP-B-0223403. The acids are commercially available.

10 The compounds of this invention may be used to treat and prevent the following disorders:

Alcoholism	Anxiety
Depression	Obsessive Compulsive Disorder
Panic Disorder	Chronic Pain
Obesity	Senile Dementia
15 Migraine	Bulimia
Anorexia	Social Phobia
Pre-Menstrual Syndrome (PMS)	Adolescent Depression
Trichotillomania	Dysthymia
Substance Abuse	

20

These disorders are herein after referred to as "the Disorders".

The present invention further provides a method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a salt of  
25 the invention to a sufferer in need thereof.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of the Disorders which comprises an admixture of a salt of the invention with a pharmaceutically acceptable carrier.

30

The present invention also provides the use of a salt of the invention for treating and/or preventing the Disorders.

The present invention also provides the use of a salt of the invention in the manufacture of a medicament for treating and/or preventing the Disorders.

5 Most suitably the present invention is applied to the treatment of depression, OCD and panic.

Compositions containing the salt of this invention may be formulated for administration by any route, and examples are oral, sub-lingual, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may, if desired, be designed to give slow  
10 release of the paroxetine salt.

The medicaments may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.  
15

The composition is usually presented as a unit dose composition containing from 1 to 200mg of active ingredient calculated on a free base basis, more usually from 5 to 100 mg, for example 10 to 50 mg such as 10, 12.5, 15, 20, 25, 30 or 40 mg by a human patient. Most preferably unit doses contain 20 mg of active ingredient calculated on a free base  
20 basis. Such a composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400 mg of active ingredient calculated on a free base basis. Most preferably the unit dose is taken once a day.

25 Preferred unit dosage forms include tablets or capsules, including formulations adapted for controlled or delayed release.

The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing. Suitable carriers for use in this  
30 invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or preservative. These agents may be utilised in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.

Specific examples of pharmaceutical compositions include those described EP-B-0223403, and US 4,007,196 in which the products of the present invention may be used as the active ingredients.

5 The following Examples illustrate the present invention:

**Example 1:** preparation of tablets

INGREDIENTS	20 mg Tablet	30mg Tablet
Paroxetine salt	20.00 mg (calc. as free base)	30.0 mg (calc. as free base)
Dicalcium Phosphate (DCP)	83.34 mg	125.0 mg
Microcrystalline Cellulose	50.67 mg	76.0 mg
Sodium Starch Glycollate	8.34 mg	12.5 mg
Magnesium Stearate	1.67 mg	2.5 mg

Commercial source of the ingredients

- |    |                               |   |                      |
|----|-------------------------------|---|----------------------|
| 10 | Dicalcium Phosphate Dihydrate | - | Emcompress or Datab* |
|    | Microcrystalline Cellulose    | - | Avicel PH 102*       |
|    | Sodium Starch Glycollate      | - | Explotab.*           |

\* Trade names

15 **Method**

1. Pass DCP through a screen and weigh it into a Planetary mixer.
2. Add 30 mesh Paroxetine salt to the bowl.
3. Add 20 mesh Avicel and Explotab and mix all the powders for 10 minutes.
4. Add magnesium stearate and mix for 5 minutes.

20 **Tablet into Pentagonal Tablets using the following punches:**

30 mg Tablet      9.5 mm      Circumcircle

20 mg Tablet      8.25 mm      Circumcircle

The tablets are made satisfactorily on a single punch or a Rotary press.

**Example 2** : preparation of tablets

INGREDIENTS	10 mg Tablet	20 mg Tablet	30mg Tablet
Paroxetine salt	10 mg (calc.as free base)	20 mg (calc.as free base)	30 mg (calc.as free base)
Sodium Starch Glycollate	2.98 mg	5.95 mg	8.93 mg
Granular Dicalcium Phosphate (DITAB) or Dicafos	158.88 mg	317.75 mg	476.63 mg
Magnesium Stearate	1.75 mg	3.50 mg	5.25 mg

**Method**

1. Paroxetine salt, Sodium Starch Glycollate and Dicalcium Phosphate Dihydrate are screened and mixed together in a suitable mixer.  
(Planetary, Cuble or High Energy Shear mixer.)
2. Add Magnesium Stearate and compress it into a tablet using a single punch or Rotary Tablet machine.

**Example 3** : Preparation of paroxetine hydrobromide.

Hydrobromic acid (1.0 ml, 48% aqueous solution) was added slowly to a stirred solution of paroxetine free base (2.1 g) in toluene (20 ml). Crystallisation commenced almost immediately and the suspension was stirred for 1 hour at ambient temperature. Finally the product was filtered, washed with toluene and dried *in vacuo*.  
Yield 2.94g.

**Example 4** : Preparation of paroxetine hydrobromide.

Hydrobromic acid (20 ml, 48% aqueous solution) was added slowly to a stirred solution of paroxetine free base (42 g) in toluene (400 ml). The resulting suspension was stirred for 1

hour at ambient temperature then for a further 1 hour at 0°C. Finally the crystalline product was filtered, washed with toluene and dried *in vacuo*.

Yield 54.03g.

m. pt 151-153°C.

5

IR nujol mull:

Bands at 3412, 1605, 1511, 1465, 1222, 1185, 1041, 1013, 929, 835, 780, 674, 573 cm<sup>-1</sup>.

X-ray powder diffractogram (Cu K<sub>2</sub>α):

10

Angle [°2θ]	Rel. Int [%]
6.4	14.1
12.8	24.1
16.6	22.0
18.1	45.0
18.3	64.3
18.6	51.8
19.4	27.0
20.2	69.3
21.3	100.0
21.9	40.3
22.3	82.8
23.0	27.8
23.6	62.1
24.0	90.5
24.5	26.6
25.5	29.1
26.0	64.1
26.5	36.1
26.7	52.3

27.4	67.3
28.0	22.9
28.4	31.1
28.8	56.5
32.3	30.1
32.6	27.6
33.6	19.9

**Example 5 : paroxetine hydrobromide**

- 5 Paroxetine base (54.9 g) was dissolved in propan-2-ol (500 ml) and the resulting solution was stirred while a mixture of hydrobromic acid (19 ml, 48% aqueous solution) and propan-2-ol (200 ml) was added slowly. The clear solution slowly crystallised and the suspension was stirred for 2 hours with cooling, filtered, washed with propan-2-ol and dried in an air oven at 40°C.
- 10 Yield 61.8 g.

**Example 6 : Preparation of paroxetine hydrobromide**

- 15 Hydrobromic acid (50 ml, 48% aqueous solution) was added slowly to a stirred solution of paroxetine base (109.8 g) in wet toluene (2000 ml). Crystallisation commenced almost immediately and the suspension was stirred for 1 hour before the product was collected by filtration. The filtration liquors were evaporated and the residual non-crystalline solid was combined with the crystalline first crop and recrystallised from hot propan-2-ol (500 ml).
- 20 The product was filtered, washed with propan-2-ol, and dried under vacuum to yield a homogenous, free-flowing white crystalline powder.

**Example 7 : Preparation of paroxetine hydrobromide**



Paroxetine base (109.8 g) was dissolved in propan-2-ol (1 L), stirred and seeded while hydrobromic acid (60 ml, 48% aqueous solution) was added slowly. The resulting crystalline suspension was stirred at ambient temperature for 3 hours, then filtered, washed with propan-2-ol, and dried under vacuum. The yield of paroxetine hydrobromide as a slightly pink solid was 120.6 g.

**Example 1 :** Preparation of paroxetine hydriodide.

Hydriodic acid (1.3ml, 55% aqueous solution) was added slowly to a solution of paroxetine base (2.1 g) in toluene (20 ml). Crystals were precipitated within a few minutes and the suspension was stirred for 2 hours at ambient temperature. Finally the product was filtered, washed with toluene and dried *in vacuo*.  
Yield 3.13g.

**Example 8 :** Preparation of paroxetine hydriodide.

Hydriodic acid (32.5 ml, 55% aqueous solution) was added slowly to a solution of paroxetine free base (52.5 g) in toluene (800 ml). Crystals were precipitated within a few minutes and the suspension was stirred for 1 hour at ambient temperature then for a further 1 hour at 0°C (ice/water bath). Finally the crystals were filtered, washed in toluene and dried *in vacuo*.  
Yield 73.9g.

**Example 9:** Recrystallisation from toluene.

Paroxetine hydriodide (70 g) was suspended in toluene (1200 ml) and heated to boiling point to form a solution. The solution was allowed to cool slowly and seeded until the product began to crystallise. After stirring for 3 more hours, the product was collected by filtration, washed with toluene and dried *in vacuo*.  
Yield 63.6 g

m.pt 158-162°C

IR nujol mull:

Bands at 3435, 1605, 1558, 1510, 1246, 1222, 1160, 1040, 926, 779, 672, 572  $\text{cm}^{-1}$ .

X-ray powder diffractogram ( $\text{CuK}\alpha$ ):

5

Angle [ $2\theta$ ]	Rel. Int [%]
6.4	60.3
12.8	47.2
15.0	17.0
18.0	43.2
18.6	45.6
20.0	87.5
20.9	75.4
22.0	100.0
23.7	79.4
24.1	49.0
25.7	67.9
26.3	41.6
26.9	45.6
27.5	24.4
28.3	36.7
28.8	40.4
30.2	25.1
30.6	17.4
31.8	30.3
32.0	22.0
33.4	15.2

**Example 10:** Preparation of crystalline salt

Hexanoic acid (0.8 ml) was added to a solution of paroxetine free base (2.3 g) in toluene (20 ml). Removal of the solvent by evaporation caused the salt to crystallise. The crystals were dried at reduced pressure.

5 Yield 2.64g.

**Example 11:** Larger scale preparation of crystalline salt.

Hexanoic acid (16 ml) was added to a solution of paroxetine free base (42 g) in toluene.

10 The solution was stirred at ambient temperature for 1 hour, then the solvent was removed by evaporation. The product crystallised and was dried at reduced pressure.

Yield 56.86g.

15 **Example 12:** Recrystallisation

Paroxetine hexanoate (46 g), prepared as in Example 2, was heated to reflux in acetonitrile (400 ml) to form a solution. This solution was cooled, stirred and seeded with crystalline paroxetine hexanoate, whereupon the product began to crystallise within 1 hour. After  
20 leaving to stand overnight it was necessary to add more acetonitrile to mobilize the product, which was then filtered, washed in acetonitrile, and dried at reduced pressure.

**Example 13:** Preparation of non-crystalline salt.

25 Hexanoic acid (0.8 ml) was added to a solution of paroxetine free base (2.1 g) in toluene (20 ml). The solvent was evaporated at 60°C to give a gum which solidified on further drying.

**Paroxetine hexanoate characterising data:**

30

m.pt 85-87°C.

IR nujol mull:

Bands at 1634, 1604, 1511, 1288, 1196, 1036, 982, 927, 912, 830, 785, 672, 601  $\text{cm}^{-1}$ .

X-ray diffractogram major peaks ( $\text{CuK}\alpha$ ):

5

Angle [ $2\theta$ ]	Rel. Int [%]
5.0	14.1
7.7	29.7
15.1	20.5
16.4	58.6
16.9	47.9
17.1	37.3
18.7	33.2
18.9	44.6
19.4	27.9
19.8	21.2
20.1	24.5
21.5	100.0
21.8	60.3
22.2	38.7
22.6	27.1
23.2	41.2
24.4	76.0
27.4	21.3
27.6	24.1
28.1	31.4
31.8	20.0

**Example 14** : Preparation of 2:1 salt of paroxetine with L-malic acid.

A solution of L-malic acid (0.8 g) in propan-2-ol (10 ml) was added to a stirred solution of paroxetine base (4.2 g) in toluene (20 ml). A crystalline solid precipitated within an hour and the mixture was diluted further with toluene (20 ml). The suspension was stirred at approximately 20°C. for a further hour, then the product was filtered, washed with toluene and dried at reduced pressure.

Yield 4.32g.

m. pt 107-109°C

10 IR nujol mull:

Bands at 3440, 1633, 1604, 1223, 1094, 1034, 982, 930, 907, 816, 784, 676, 581  $\text{cm}^{-1}$ .

X-ray powder diffractogram major peaks ( $\text{CuK}\alpha$ ):

Angle [ $2\theta$ ]	Rel. Int [%]
3.6	27.5
5.5	26.2
14.6	15.8
15.7	20.7
17.2	55.8
17.5	53.4
17.9	68.3
18.6	96.8
19.1	60.1
19.6	77.0
19.9	50.1
20.2	43.7
21.0	86.6
21.6	42.9
22.3	29.2
22.9	73.1

23.2	85.8
23.5	59.5
24.2	60.5
27.1	40.3
27.7	34.1
28.9	45.6
30.1	34.5
31.1	29.0

**Example 15 :** Preparation of 1:1 salt of paroxetine with L-malic acid.

- 5 A solution of L-malic acid (0.8 g) in propan-2-ol (10 ml) was mixed with a stirred solution of paroxetine free base (2.1 g) in toluene (20 ml). The resulting solution was diluted with ethyl acetate (20 ml) and hexane (40 ml) to precipitate an oil, which was separated from the solvent by decanting and then triturated in diethyl ether (50 ml) to form a solid product. After stirring for another hour, the product was filtered, washed with diethyl ether and dried *in vacuo*.
- 10 Yield 1.21 g.

IR nujol mull:

Bands at 1605, 1464, 1182, 1036, 929, 831, 540  $\text{cm}^{-1}$ .

- 15 **Example 16:** Preparation of non-crystalline paroxetine L-aspartate

- A solution of paroxetine base in toluene (5 ml, 6.38 mmol) was added to a suspension of L-aspartic acid (0.85 g, 6.38 mmol) in hot methanol (45 ml). The mixture was heated at reflux for 30 minutes, allowed to cool, filtered and the solvent was removed at reduced pressure. The residual oil was diluted with toluene (30 ml) and the solvent removed at reduced pressure. Trituration with diethyl ether (c. 20 ml) and filtration under nitrogen gave an off-white solid which was washed with diethyl ether ( $2 \times 10$  ml) and dried. Yield 2.29 g.

$^1\text{H}$  NMR (DMSO) showed a ratio between L-aspartic acid and paroxetine of 1:1.

IR nujol mull:

Bands at 1604, 1464, 1377, 1224, 1186, 1038, 931, 832, 722, 658, 540.

5 **Example 17** : Preparation of crystalline 1:1 paroxetine L(+)-aspartate

A suspension of L(+)-aspartic acid in a mixture of propan-2-ol (90 ml) and water (30 ml) was gently heated and paroxetine free base (4.2g) in toluene (10 ml) was added so that the acid dissolved. The solvent was removed by evaporation and toluene (100 ml) was twice added to the residue and evaporated. The oily residue was triturated and stirred in a mixture of propan-2-ol (100 ml) and hexane (50 ml) and the product crystallised within a few hours. Finally the crystals were collected by filtration, washed with hexane and dried at reduced pressure.

15 m.pt 112-115°C

IR nujol mull:

Bands at 1634, 1583, 1506, 1246, 1206, 1167, 1137, 1045, 933, 834, 786, 722, 654 cm<sup>-1</sup>.

20 X-ray powder diffractogram (CuK<sub>2</sub>α):

Angle [°2θ]	Rel. Int [%]
6.9	5.3
13.6	13.7
13.9	11.0
17.4	32.5
17.9	20.9
19.0	100.0
19.5	98.9
20.2	21.0
20.7	28.0

22.2	54.6
22.6	26.3
23.1	17.7
23.6	26.2
24.4	20.2
26.0	26.0
27.2	35.3
27.7	35.1
28.1	30.5
32.5	25.2

**Example 18 :** Preparation of paroxetine adipate 1:1 salt.

A solution of paroxetine base in toluene (2.1 g in 5 ml) was mixed with a solution of adipic acid (0.93 g) in methanol (15 ml). The solvent was removed at reduced pressure, replaced with fresh toluene (10 ml), and evaporated again. The residue was triturated with diethyl ether (15 ml) and stirred under nitrogen for 16 hours to produce a white crystalline solid, which was filtered, washed with diethyl ether ( $2 \times 10$  ml) and dried in a vacuum desiccator. Yield = 2.62g,

10

**Example 19 :** Preparation of paroxetine adipate 1:1 salt.

A solution of paroxetine base in toluene (42 g in 100 ml) was added to a solution of adipic acid (18.64 g) in methanol (300 ml). The solvent was removed at reduced pressure, replaced with fresh toluene (100 ml), and evaporated again. The residue was triturated with cyclohexane (350 ml) and stirred under nitrogen for 18 hours to crystallise. The product, was filtered, washed with cyclohexane ( $3 \times 100$  ml) and dried. Yield 60.83g. m.p. 89 - 93°C.

20 IR nujol mull:

Bands at:

1712, 1636, 1506, 1466, 1377, 1275, 1221, 1191, 1143, 1034, 929, 833, 540  $\text{cm}^{-1}$ .



X-ray powder diffractogram major peaks (CuK<sub>2</sub> $\alpha$ ):

Angle [ $^{\circ}2\theta$ ]	Rel. Int [%]
5.7	10.3
10.7	23.1
11.3	15.8
12.1	27.2
12.9	14.4
14.3	35.4
15.0	15.3
16.7	77.4
17.2	96.1
17.6	32.0
18.2	100.0
18.8	32.9
19.1	60.5
20.0	75.7
20.1	78.0
21.3	55.3
21.6	31.3
22.1	23.2
22.9	52.80
23.9	63.1
24.2	38.2
24.9	91.3
25.3	27.2
26.1	75.7
27.0	41.1
28.1	19.1
29.0	34.9

29.8	12.5
30.2	16.8
30.8	12.6
31.7	17.2
32.3	24.3
33.2	19.7
33.5	22.3

**Example 20 :** Preparation of paroxetine adipate.

5 A solution of paroxetine base in toluene (2.1 g in 5 ml) was mixed with a solution of adipic acid (0.467 g) in methanol (15 ml). The solvent was removed at reduced pressure, replaced with fresh toluene (10 ml), and evaporated again. The residue was triturated with diethyl ether (15 ml) to produce a white crystalline solid, which was filtered, washed with diethyl ether (2 × 10 ml) and dried in a vacuum desiccator.

Yield = 2.45g,

10

**Example 21 :** Preparation of paroxetine adipate 2:1 salt.

15 A solution of paroxetine base in toluene (44.3 g in 105 ml) was added to a solution of adipic acid (9.78 g) in methanol (150 ml). The solvent was removed at reduced pressure, replaced with fresh toluene (100 ml), and evaporated again. The residue was triturated with diethyl ether (300 ml) to crystallise, then filtered, washed with diethyl ether (2 × 100 ml) and dried in a desiccator.

Yield 51.55g. m.p. 123 - 126°C.

20 IR nujol mull:

Bands at 1630, 1504, 1490, 1464, 1378, 1275, 1269, 1242, 1220, 1191, 1141, 1105, 1038, 986, 935, 842, 784, 721, 677, 622, 582, 536  $\text{cm}^{-1}$ .

X-ray powder diffractogram major peaks ( $\text{CuK}_{2\alpha}$ ):

Angle [ $^{\circ}2\theta$ ]	Rel. Int [%]
11.5	10.6
16.4	14.2
18.9	42.2
19.7	100.0
20.5	23.5
21.0	21.3
21.4	20.0
22.0	20.4
23.3	33.2
26.4	21.4
26.9	27.9
27.4	17.9
28.7	10.6

#### 5 Example 22

Palmitic acid (0.75 g) was dissolved in toluene (10 ml) and mixed with a solution of paroxetine base (1 g) in toluene. The mixture was stirred at approximately 20°C for 1 hour then the solvent was removed by evaporation during which process the product crystallised.

10 The crystals were dried at reduced pressure.

#### Example 23

15 Palmitic acid (37.5 g) was dissolved in toluene (500 ml) and mixed with a solution of paroxetine base (52.5 g) in toluene (150 ml). The solvent was slowly removed by evaporation to cause the product to crystallise. The product, a white crystalline solid, was dried in a vacuum desiccator.

Yield 85.92g.

**Example 24 : Recrystallisation.**

- 5 Paroxetine palmitate (60 g) was dissolved in acetone (500 ml) by heating to reflux, and the solution allowed to cool. Seeds were added, whereupon crystallisation began almost immediately, and the mixture was stirred for 3 hours at approximately 20°C, adding further acetone as necessary to keep the mixture at a suitable consistency for efficient stirring. The product was collected by filtration, washed with acetone and dried at reduced pressure.
- 10 Yield 41.5g.

m.pt 77-79°C.

IR nujol mull:

- 15 Bands at 1644, 1464, 1206, 1042, 934, 836, 822, 794, 785, 720, 604, 540  $\text{cm}^{-1}$ .

X-ray powder diffractogram major peaks ( $\text{CuK}_{2\alpha}$ ):

Angle [ $2\theta$ ]	Rel. Int [%]
11.4	7.1
16.3	9.8
17.8	13.1
19.6	100.0
21.8	46.0
22.5	38.0
22.8	35.2
22.9	30.6
27.8	19.1

20

**Example 25 : Preparation of crystalline stearate salt.**

- 5 Stearic acid (1.6 g) was dissolved in toluene (10 ml) and mixed with a solution of paroxetine base (2.1 g in toluene (20 0ml). The mixture was stirred at approximately 20°C for 1 hour then the solvent was removed by evaporation during which process the product crystallised. The crystals were dried at reduced pressure.  
Yield 3.62 g.

**Example 26 :** Larger scale preparation of crystalline salt.

- 10 Stearic acid (32 g) was dissolved in toluene (300 ml) with heating to form a solution, and mixed with a solution of paroxetine base (42 g) in toluene (100 ml). The solvent was slowly removed by evaporation to cause the product to crystallise. The product, a white crystalline solid, was dried in a vacuum desiccator.  
Yield 70.31 g.

**Example 27 : Recrystallisation.**

5 Paroxetine stearate (60 g) was dissolved in acetone (800 ml) by heating to reflux, and the solution allowed to cool. The mixture started to crystallise and was stirred for 3 hours at approximately 20°C, adding further acetone as necessary to keep the mixture at a suitable consistency for efficient stirring. The product was collected by filtration, washed with acetone and dried at reduced pressure.

Yield 44.32 g.m. pt 80-82°C.

10 IR nujol mull:

Bands at 1641, 1510, 1464, 1246, 1044 934 913, 836, 787, 721, 677, 579  $\text{cm}^{-1}$ .

X-ray powder diffractogram major peaks ( $\text{CuK}\alpha$ ):

Angle [ $2\theta$ ]	Rel. Int
6.5	48.1
10.9	76.1
13.0	25.6
17.2	66.3
17.4	64.7
19.6	100.0
20.6	31.1
21.7	64.7
22.9	52.3
25.3	20.0
27.9	22.7
28.6	16.8
30.7	11.5
32.9	16.0

15 **Example 28 : Preparation of paroxetine ethylenediaminetetraacetic acid 1:1 salt**

- A solution of paroxetine base in toluene (1.05 g in 2.5 ml) was added to a suspension of ethylenediaminetetraacetic acid (0.93 g) in methanol (200 ml) and the mixture stirred for 1 hour at reflux temperature. The mixture was filtered while hot and the solvents removed under reduced pressure. The residue was then diluted with toluene (30 ml) and the solvents again removed under reduced pressure. The solid was triturated with diethyl ether (50 ml) and the product collected by filtration as an off-white solid. After drying, the yield was 1.16g.

IR (Nujol): 1634, 1184, 1036, 831, 540  $\text{cm}^{-1}$

10

X-Ray ( $\text{CuK}_{2\alpha}$ ) powder diffractogram, major peaks with relative intensity greater than 15%.

Angle [ $2\theta$ ]	Rel. Int [%]
13.4	16.6
14.2	19.9
16.4	41.6
17.2	53.5
17.9	77.9
20.1	83.9
22.2	100.0
23.4	62.0
24.6	89.6
25.8	60.6
26.8	63.0
29.0	47.9
29.5	46.6
30.3	34.3
32.2	44.2
33.1	32.2

- 15 **Example 29** : Preparation of paroxetine-2-naphthoate

-29-

- A solution of paroxetine base in toluene (2.1 g in 10 ml) was added to a solution of 2-naphthoic acid (1.1 g) in methanol (50 ml). The reaction mixture was stirred at approximately 20°C and the solvents removed by low pressure distillation to afford a glassy
- 5 white solid of non-crystalline paroxetine-2-naphthoate. This solid was triturated with heptane to afford a white crystalline solid, which was filtered, washed with heptane and dried at reduced pressure .

Yield 2.1 g

- 10 Melting point 118-123°C



IR nujol mull:

Bands at 1490, 1463, 1377, 1218, 1039, 933, 792, 582, 539  $\text{cm}^{-1}$ .

X-ray powder diffractogram (Cu K $\alpha$ ):

5

Angle [ $2\theta$ ]	Rel. Int [%]
6.4	5.9
8.5	0.4
9.9	6.3
11.2	8.1
11.5	4.2
13.4	19.6
14.6	10.7
15.1	25.8
16.1	28.7
16.5	30.5
17.9	34.9
18.6	65.2
19.0	77.8
19.5	100.0
19.9	79.3
20.5	74.9
21.4	29.4
22.2	42.5
22.6	31.4
23.2	41.4
23.4	45.1
23.7	44.0
23.9	39.1
24.3	27.3

24.6	23.8
24.9	20.2
25.4	13.4
27.1	51.1
27.8	42.7
28.3	26.3
29.3	20.8
29.6	23.1
30.5	18.6
31.3	14.5
32.5	15.3
33.1	17.3

**Example 30: Preparation of paroxetine 1-naphthoate**

- 5 To a solution of paroxetine base (4.2 g) in diethyl ether (20 ml) was added a solution of 1-naphthoic acid in diethyl ether (40 ml) and the mixture was stirred at ambient temperature. The solvent was removed by evaporation at low pressure to produce non-crystalline paroxetine-1-naphthoate as a pale brown solid. To this solid was added a mixed solution of propan-2-ol (8 ml) and diethyl ether (30 ml), and the mixture was stirred and heated at
- 10 gentle reflux. On cooling, crystalline paroxetine-1-naphthoate precipitated from the solution as a white solid, which was isolated by filtration, and dried under vacuum.

Melting point 128-130°C

- 15 IR nujol mull:

Bands at 1630, 1538, 1407, 1269, 1216, 919, 847, 753, 673  $\text{cm}^{-1}$ .

X-ray powder diffractogram (Cu K $\alpha$ ):

Angle [ $2\theta$ ]	Rel. Int [%]
7.8	1.4
8.6	4.1
12.0	5.7
12.6	4.1
13.2	9.5
13.7	7.0
15.0	3.0
16.1	13.9
17.2	100.0
18.0	3.3
18.4	14.9
19.0	61.8
19.6	4.2
30.3	25.3
20.9	7.8
21.3	22.9
22.0	34.4
22.4	25.7
22.7	9.2
23.0	15.7
23.3	4.9
24.2	37.6
25.3	20.5
25.7	5.4
26.1	23.5
26.6	9.9
26.9	13.5

27.5	10.0
28.2	17.8
29.0	5.5
29.2	7.9
29.8	9.8
30.0	5.4
31.2	11.5
31.8	5.6
32.2	4.9
32.7	6.6
33.2	11.9
33.9	9.9
34.5	7.5

**Example 31: Preparation of paroxetine-l-naphthalenesulphonate**

5 A solution of l-naphthalenesulphonate (2.95 g) in toluene (20 ml) was added to a flask containing paroxetine base (4.2 g) and stirred at approximately 20°C to form a solution. Diethyl ether (20 ml) was added, and the mixture heated gently then cooled, whereupon paroxetine-l-naphthalenesulphonate precipitated as a white crystalline solid. The product was isolated by filtration, and dried under vacuum.

Yield 3.6 g

10

IR nujol mull:

Bands at 3052, 2360, 1605, 1394, 1219, 1176, 1092, 845, 775, 621  $\text{cm}^{-1}$ .

X-ray diffractogram major peaks (Cu K $\alpha$ ):

Angle [ $2\theta$ ]	Rel. Int [%]
5.5	100.0
8.3	1.9
9.5	6.7
11.1	3.7
11.5	2.2
12.9	7.2
13.7	5.6
14.7	12.0
15.2	17.0
16.1	16.4
16.6	18.5
17.0	36.7
17.6	19.3
18.7	26.7
19.6	45.2
19.8	44.2
20.3	46.1
21.3	50.2
21.8	31.7
22.3	27.0
22.8	23.8
23.4	32.2
24.5	33.0
25.6	14.3
26.0	14.3
28.2	8.5
28.6	4.5

29.7	5.4
30.4	3.9
31.2	2.2
32.3	0.7

**Example 32** : Preparation of paroxetine pamoate 1:1 salt.

- 5 A solution of paroxetine base in toluene (5 ml, 2.10 g) was added to a solution of pamoic acid (2.48 g) in pyridine (40 ml), and the mixture was stirred at ambient temperature for 30 minutes. The solvent was then removed by distillation at reduced pressure, the residual oil diluted with toluene (30 ml) and the solvent again removed by distillation at reduced pressure. This procedure was repeated two more times. The solid product was washed
- 10 with hot diethyl ether (c. 100 ml  $\times$  3), and filtered under nitrogen to give a pale yellow solid. The product was washed twice more with diethyl ether (2  $\times$  100 ml), and then with methanol (30 ml), and finally dried under vacuum.

Yield = 3.27 g,

15

IR nujol mull:

Bands at 1636, 1558, 1508, 1459, 1377, 1183, 1036, 830, 722  $\text{cm}^{-1}$ .

- 20 **Example 33** : Preparation of paroxetine pamoate 2:1 salt.

- A solution of paroxetine base in toluene (10 ml, 4.2 g) was added to a solution of pamoic acid (2.48 g) in pyridine (40 ml). The mixture was stirred at ambient temperature for 30 minutes. The solvent was then removed by distillation at reduced pressure, the residual oil
- 25 diluted with toluene (30 ml) and the solvent again removed by distillation at reduced pressure. This procedure was repeated two more times. The solid product was washed with diethyl ether (c. 50 ml), and filtered under nitrogen to give a white solid. This solid was washed twice more with diethyl ether (2  $\times$  10 ml), and then dried under vacuum.

Yield 6.7 g.

IR nujol mull:

5 Bands at 1641, 1461, 1377, 1181, 1035, 829, 757  $\text{cm}^{-1}$ .

**Example 34 - Preparation of non-crystalline paroxetine D-gluconate**

10 An aqueous (45-50% by weight) solution of D-gluconic acid (3.39 g, 2.7 ml) was added to a flask containing a solution of paroxetine base (2.1 g) in ethyl acetate (10 ml). The mixture was stirred to form a clear solution, and the solvents were removed by distillation at reduced pressure to produce paroxetine D-gluconate as a non-crystalline solid.

15 Yield = 2.5 g

**Example 35 - Crystallisation of paroxetine D-gluconate**

20 A mixture of non-crystalline paroxetine D-gluconate (1.0 g) and acetone (9 ml) was heated to reflux to form a clear solution and then allowed to cool slowly to ambient temperature (approximately 22°C). The solution was stirred, seeded with crystals of paroxetine D-gluconate (which were initially prepared by trituration of the non-crystalline salt), and cooled with ice. A white crystalline product precipitated from the solution, and after  
25 several hours was collected by filtration, washed with acetone and dried at reduced pressure over phosphorous pentoxide.

Yield = 0.7 g

Melting point = 136-140°C

30

IR nujol mull:

Bands at 3469, 2360, 1629, 1575, 1340, 1222, 1088, 926, 772, 719, 668  $\text{cm}^{-1}$ .

X-ray diffractogram major peaks (Cu K $\alpha$ ):

Angle [ $2\theta$ ]	Rel. Int [%]
3.6	11.6
4.9	9.5
6.1	1.7
7.8	5.0
9.0	3.9
9.8	3.9
12.3	8.7
14.7	8.4
15.1	17.2
15.7	64.8
16.5	53.5
16.9	47.8
17.4	18.4
17.8	17.9
18.3	45.1
18.8	34.7
19.4	83.9
19.7	40.3
21.2	100.0
21.7	23.7
22.4	59.3
22.8	56.8
23.6	32.8
24.5	43.4
25.9	9.5
27.1	21.7
27.4	39.4



28.1	30.4
28.8	20.0
30.0	16.7
30.9	27.4
31.3	24.6
32.1	12.8
32.7	12.1
33.7	21.0
34.6	44.4
34.7	45.6

**Example 36 :** Preparation of crystalline hydroxynaphthoate salt

- A solution of paroxetine base in toluene (2.1 g in 5.0 ml) was added to a solution of 1-hydroxy-2-naphthoic acid (1.20 g) in a mixture of toluene (15 ml) and methanol (3 ml). The solvents were removed under reduced pressure, then the residue was taken up in fresh toluene (20 ml) and the solvent evaporated once more under reduced pressure. Trituration of the residue with diethyl ether (50 ml) gave the product as a white crystalline solid which was collected by filtration and dried.
- Yield 2.17 g, 65%

**Example 37 : Large scale preparation of crystalline salt**

A solution of paroxetine base in toluene (62.6 g in 150.0 ml) was added to a solution of 1-hydroxy-2-naphthoic acid (36.0 g) in a mixture of toluene (400 ml) and methanol (105 ml).

- 5 The solvents were removed under reduced pressure, then the residue was taken up in fresh toluene (150 ml) and the solvent evaporated once more under reduced pressure. Trituration of the residue with diethyl ether (1000 ml) produced a white crystalline solid which was collected by filtration and dried under reduced pressure.

Yield 98.83 g, 99.8%

10

mp : 169-170°C

IR (Nujol) : Bands at 1630, 1566, 1504, 1470, 1404, 1309, 1269, 1241, 1218, 1189, 1142, 1105, 1076, 1038, 933, 887, 840, 830, 790, 776, 725, 676, 623, 606, 580, 538 cm<sup>-1</sup>

- 15 X-Ray diffractogram, major peaks with Rel. Int > 15% (CuK<sub>2</sub>α)

Angle [°2θ]	Rel. Int [%]
10.1	19.1
13.3	21.3
16.1	15.5
16.8	29.2
18.4	46.3
18.6	51.7
18.8	38.5
19.4	66.4
19.8	93.5
20.7	100.0
21.3	19.8
22.4	54.3
23.2	32.6
23.6	52.4

25.0	15.7
26.7	42.1
27.2	16.3
27.9	63.9
29.0	15.1
30.5	19.5
33.4	19.6

**Example 38: Preparation of paroxetine 3-hydroxy-2-naphthoate**

A solution of paroxetine base in toluene (2.1 g in 5.0 ml) was added to a solution of 3-hydroxy-2-naphthoic acid (1.20 g) in a mixture of toluene (15 ml) and methanol (3 ml). The solvents were removed under reduced pressure, then the residue was diluted with toluene (20 ml) and the solvents again removed under reduced pressure. The residual material was triturated with hexane fractions (50 ml) and the resulting off-white solid was collected by filtration and dried.

Yield 2.83 g, 86%

IR (Nujol) : 1649, 1510, 1182, 1036, 830, 779, 738, 595, 539  $\text{cm}^{-1}$

**Example 39 : Preparation of paroxetine salicylate**

A solution of paroxetine base (4.2 g) in toluene (90 ml) was added to a suspension of salicylic acid (1.76 g) in water (28 ml), and the mixture was heated to reflux to form a solution. The water was removed by heating at reflux in a Dean and Stark apparatus, then the mixture was cooled and the solvent decanted. Residual solvent was removed by drying at reduced pressure and the resulting solid was stirred with heptane overnight, filtered under an atmosphere of nitrogen and dried to produce paroxetine salicylate as a pinkish powder.

Yield 3.9 g

IR spectrum (nujol mull):

Bands at 2966, 2359, 1631, 1590, 1485, 1138, 931, 830, 705  $\text{cm}^{-1}$ .

**Example 40**

A round bottom flask was charged with paroxetine hydrochloride anhydrate (4.03 g, 11 mmols) and propan-2-ol (150 ml), and the mixture was heated to ensure total dissolution of paroxetine hydrochloride. To this solution was added, in an atmosphere of nitrogen, 4-hydroxybutyric acid sodium salt (1.39 g, 11 mmols) in ethanol (100 ml). The reaction mixture was stirred and a white precipitate formed. This precipitate was filtered and the filtrate was concentrated at a reduced pressure to afford a pink glassy solid of amorphous paroxetine 4-hydroxybutyrate.

Yield = 5.01 g

**Example 41: Recrystallisation of paroxetine 4-hydroxybutyrate**

A round bottom flask equipped with a condenser was charged with paroxetine 4-hydroxybutyrate prepared in example 1 (2.0 g) and ethyl acetate (15 ml). The reaction was brought to reflux temperature, cooled to room temperature and seeded with crystals of paroxetine 4-hydroxybutyrate. The reaction was cooled to 0-4°C whereupon crystallisation commenced. After stirring for 1 hour, the crystals were collected by filtration under a nitrogen atmosphere and dried at a reduced pressure over phosphorous pentoxide to afford crystalline paroxetine 4-hydroxybutyrate.

Yield = 1.51 g

**Example 42: Recrystallisation of paroxetine 4-hydroxybutyrate**

Further samples of crystalline paroxetine 4-hydroxybutyrate were prepared by adding amorphous paroxetine 4-hydroxybutyrate in the minimum amount of refluxing solvent, for example toluene and  $\text{CHCl}_3$ . The reaction was subsequently cooled to 0-4°C and seeded to induce crystallisation. The crystals were collected under an atmosphere of nitrogen and dried over  $\text{P}_2\text{O}_5$  at reduced pressure to afford crystalline paroxetine 4-hydroxybutyrate.

Molar ratio of paroxetine : 4-hydroxybutyric acid by  $^1\text{H}$  NMR = 1:1

Melting Point = 91-93 °C

5 IR (Attenuated total reflection) :

Sample recrystallised from ethyl acetate : bands at *circa* 1646, 1545, 1493, 1392, 1219, 1194, 1160, 1135, 1037, 948, 931, 912, 829, 806, 785, 763, 660, 601, 557  $\text{cm}^{-1}$ .

10 Sample recrystallised from toluene : bands at *circa* 1651, 1538, 1512, 1504, 1488, 1466, 1396, 1381, 1267, 1218, 1186, 1138, 1055, 932, 837, 798, 783, 676, 612, 580, 556  $\text{cm}^{-1}$ .

Sample recrystallised from  $\text{CHCl}_3$  : bands at *circa* 1651, 1538, 1511, 1489, 1467, 1396, 1220, 1189, 1133, 1075, 1034, 948, 927, 908, 837, 828, 806, 756, 743, 666, 612, 600, 580, 560  $\text{cm}^{-1}$ .

15

X-ray powder diffractogram (Cu K2 $\alpha$ ):

Angle [ $2\theta$ ]	Rel. Int [%]
3.6	4.7
5.1	2.1
7.7	100.0
9.0	1.1
9.5	1.5
10.2	1.7
12.5	4.6
13.1	2.3
15.6	9.7
16.1	16.3
16.8	3.8
17.5	44.2

18.2	22.3
18.9	11.6
19.3	3.8
20.5	12.9
21.4	8.5
22.2	67.7
22.2	67.7
23.4	66.3
23.7	42.8
24.3	49.4
25.2	8.0
25.6	8.2
26.1	5.2
26.5	5.5
27.2	4.8
28.3	25.7
28.5	49.1
29.0	9.3
29.4	6.8
29.7	6.9
30.9	4.4
31.4	11.4
32.1	6.3
33.0	14.0
34.4	6.1

**CLAIMS**

1. A salt of paroxetine with an acid selected from the group consisting of  
5 hydrobromic, hydroiodic, hexanoic, malic, aspartic, adipic, palmitic, stearic, ethylenediaminetetraacetic (EDTA), naphthoic, naphthalenesulphonic, pamoic, gluconic, salicylic, hydroxynaphthoic and hydroxybutyric acids.
- 2 A salt of paroxetine with malic, aspartic, adipic, EDTA or pamoic acid, in which  
10 the ratio of paroxetine to the acid (by mole) is 1:1 or 2:1, in the case where the ratio is less than the theoretical maximum, the salt is a hydrogen salt or a mixed salt with a cation other than hydrogen.
3. A salt of paroxetine with malic, aspartic or gluconic acid, in which the acid is in the  
15 D or L-form or a racemic mixture thereof.
4. A compound according to any one of the preceding claims, in non-crystalline form.
5. A compound according to claim 1, 2, or 3, in crystalline form.  
20
6. A process for the preparation of a compound as claimed in any preceding claim, by precipitation, spray drying or freeze drying a solution of a paroxetine salt, or by vacuum drying of oils of a paroxetine salt, or solidification of a melt of a paroxetine salt.
- 25 7. A process for the preparation of a compound as claimed in any one of claims 1 to 5, by crystallization or re-crystallization from a solution of a paroxetine salt.
8. A process according to claim 6 or 7 in which the solution, oil or melt of a paroxetine salt is prepared by treating paroxetine free base or an organic acid salt thereof  
30 with an acid or a salt thereof (including a hydrogen salt), or by contacting a paroxetine hydrogen salt with a cation other than hydrogen.



9. A method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a compound according to any one of claims 1 to 5 to a sufferer in need thereof.

5

10. A pharmaceutical composition for use in the treatment and/or prevention of the Disorders which comprises a compound according to any one of claims 1 to 5 or a product of the process of any one of claims 6 to 8, together with a pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 99/02588

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/12 A61K31/4525

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 188 081 A (FERROSAN AS) 23 July 1986 (1986-07-23) page 3, line 25 - line 28; claims 1,4-7 ---	1,9,10
X	EP 0 810 224 A (ASAHI GLASS CO LTD) 3 December 1997 (1997-12-03) column 1, line 30 - line 31; claim 1 ---	1,9,10
A	EP 0 223 403 A (BEECHAM GROUP PLC) 27 May 1987 (1987-05-27) page 4, line 8 - line 12; examples ---	1,9,10
A	WO 98 01424 A (BORZA ISTVAN ;CZIBULA LASZLO (HU); DOBAY LASZLO (HU); HARSANYI KAL) 15 January 1998 (1998-01-15) page 4, line 25; claim 1 --- -/--	1,9,10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 October 1999

Date of mailing of the international search report

04/11/1999

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02588

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 98 56787 A (SYNTHON B V) 17 December 1998 (1998-12-17) abstract ---	1,9,10
E	WO 99 40084 A (CROWE DAVID ;KEEFFE DEIRDRE O (GB); SMITHKLINE BEECHAM PLC (GB); U) 12 August 1999 (1999-08-12) abstract -----	1,9,10

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 02588

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 9  
is directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compounds.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02588

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0188081	A	23-07-1986	AU 580820 B	02-02-1989
			AU 5074985 A	12-06-1986
			DE 3585607 A	16-04-1992
			DK 562585 A,B,	05-06-1986
			JP 1881453 C	21-10-1994
			JP 5086763 B	14-12-1993
			JP 61148121 A	05-07-1986
			US 4745122 A	17-05-1988
EP 0810224	A	03-12-1997	CA 2206592 A	30-11-1997
			JP 10045756 A	17-02-1998
EP 0223403	A	27-05-1987	AU 593295 B	08-02-1990
			AU 6433286 A	30-04-1987
			BG 61323 B	30-05-1997
			CA 1287060 A	30-07-1991
			CZ 9103910 A	19-01-1994
			CY 1743 A	17-02-1995
			DE 3688827 A	09-09-1993
			DE 3688827 T	31-03-1994
			DK 61091 A	05-04-1991
			DK 508786 A	26-04-1987
			ES 2058061 T	01-11-1994
			FI 864320 A,B,	26-04-1987
			HK 125993 A	19-11-1993
			IE 59901 B	20-04-1994
			JP 1918281 C	07-04-1995
			JP 6047587 B	22-06-1994
			JP 62129280 A	11-06-1987
			NZ 218047 A	29-03-1989
			PT 83608 A,B	01-11-1986
			US 4721723 A	26-01-1988
WO 9801424	A	15-01-1998	HU 9601857 A	28-05-1998
			AU 3631197 A	02-02-1998
			EP 0923554 A	23-06-1999
WO 9856787	A	17-12-1998	US 5874447 A	23-02-1999
			AU 3108097 A	30-12-1999
WO 9940084	A	12-08-1999	NONE	

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